



Protocol Deviations Guidance

Purpose

The purpose of this guidance document is to outline the types of protocol deviations for research with human subjects at Weill Cornell Medicine (WCM) and their respective reporting requirements and review processes.

This guidance reinforces the responsibility of investigators and research staff to follow the written protocol as provided by the sponsor and approved by the IRB. Strict adherence to the protocol is more likely to protect human subjects and preserve the integrity of the data and research.

Applicability

This guidance applies to all WCM IRB approved human subject research protocols including protocols granted expedited approval. This guidance does not apply to protocols deemed by the IRB to be exempt from review. If the WCM site is a lead/coordinating site, then protocol deviation reports submitted from other sites must be sent to the WCM IRB and included on the protocol-specific Deviation Log.

Types of Protocol Deviations and Reporting Requirements

The WCM Office of Research Integrity encourages sponsors and investigators to develop protocols that include flexibility in research methods where possible without adversely affecting subject safety or the scientific data (e.g. ability to answer the research question and systematically collect data). Flexibility that is built into the protocol will reduce the number of changes that have to be reviewed by the IRB and should reduce the number of incidents of deviations and non-compliance by investigators. Please note: Human gene transfer trials must also submit protocol deviations to the Institutional Biosafety Committee, per the IBC policies. The IRB will forward applicable submission to the IBC. If the WCM Data and Safety Monitoring Committee is used, the study team must submit a PDF of the protocol deviation to dsmc@med.cornell.edu.

A. Planned Protocol Deviations

Planned protocol deviations, also defined as protocol exceptions, are single and specific waivers affecting one subject. They are not intended to be a permanent change to the protocol and are not intended to be requested on a regular basis, i.e. multiple requests for the same deviation. If multiple requests are submitted for the same deviation or to the same protocol, the Principal Investigator may be required to submit an amendment to the WCM IRB for review.

All planned deviations must be approved by the study sponsor (if applicable) prior to submitting to the WCM IRB. Investigator-Initiated Trial (IIT) planned protocol deviations that would change dosing, waive inclusion/exclusion criteria or otherwise potentially impact subject risk, require written concurrence by a department faculty member with appropriately related expertise who is not a principle investigator or co-investigator of the study. All protocol deviations must be reported to the FDA in accordance with FDA regulations as required.

Upon receipt, all planned protocol deviation requests will receive a regulatory pre-review by the IRB office within one business day. The request will then be forwarded to an IRB member for review, and a determination will then be made within two business days for most requests, provided all appropriate documentation is submitted to the IRB. Determinations may include approval, approval with modifications or stipulations, requirement for full board review, or denial. *Any request for rushed IRB review (less than 48 hours) must be accompanied by emergency contact information for the study PI. All IRB-approved planned protocol deviations must also be entered into the Protocol Deviation Log.*

The following are examples of planned protocol deviations (Please note, this list is not intended to be comprehensive):

1. Waiver of inclusion/exclusion criteria
 1. Age
 2. Laboratory or imaging screening
 3. Drug washout schedule
 4. Disease pre-treatment
2. Deviation from dosage scheduling
3. Deviation from planned premedication due to subject allergy or intolerance (i.e. Tylenol vs. Advil)
4. Deviation from laboratory testing/imaging monitoring and follow up schedule
5. Changes to a survey instrument

B. Unpreventable Protocol Deviations that are identified before they occur.

These are deviations from the protocol that an investigator, research staff and/or other party involved in the conduct of the research are able to identify before they occur, but cannot prevent from occurring.

Examples:

1. A research subject called out of town and informs the investigator that she cannot attend the study visit scheduled for the next day. The investigator knows in advance that the deviation will occur, but it is not under the investigator's control, and it is not the investigator's intent to deviate from the protocol.
2. A study visit falls on a holiday or day when the clinic is closed.

All unpreventable protocol deviations must be entered into the protocol deviation log. Such deviations do NOT require IRB review and approval.

C. Unplanned Protocol Deviations

These are unplanned deviations from the protocol that were unintended by the researcher. Such unplanned deviations are usually the result of a mistake or failure on behalf of the research team or the research subject to follow the approved study protocol.

Examples of unplanned deviations:

1. Investigator does not perform a protocol-required physical
2. A subject fails to correctly self-administer the study device or drug.
3. A coordinator's failure to perform a protocol-required blood test on subjects.

All unplanned deviations must be entered into the protocol deviation log.

Unplanned deviations must be reviewed by the PI upon discovery to determine the following:

- **The root cause of the deviation,**
- **Whether or not the deviation(s) constitutes an unanticipated problem involving risks to subjects or others,**
- **Whether or not the deviation(s) constitutes serious or continuing non-compliance and need to be reported as described in the WCM Immediate Reporting Policy.**

A Protocol deviation that represents a failure to follow the IRB approved protocol or IRB policies, and is due to the action or inaction of the investigator or researcher, must be immediately reported within 24 hours of discovery if BOTH of the following conditions are applicable:

1. The deviation had the potential to negatively impact subject safety or integrity of study data (ability to draw conclusions from the study data), or affect the subject's willingness to participate in the study
AND
2. The deviation places WCM subjects at greater risk of harm (including physical, psychological, economic, legal or social harm).

Please refer to the Human Research Protections Program Immediate Reporting Policy in the Policies section of the IRB website for full instructions on immediate reporting.

D. Emergent protocol deviations to eliminate apparent immediate hazards

These types of deviations are performed in reaction to a perceived hazard, such as the occurrence of an unexpected serious adverse event. They are intentional, but they are done to prevent harm to subjects in a time-sensitive situation, as specifically allowed by the Department of Health and Human Service regulations at 45 CFR §46.108(a)(3) and 21 CFR §56.108(a)(4) .

Emergent protocol deviations MUST be reported to the IRB within 24 hours.

Note regarding emergent initiation of an investigational product or protocol: Both federal regulations at 45 CFR §46.108(A) and §46.116 (F) and WCM policy do not permit research activities to be started, or IRB approved research to be changed, without prior IRB review except when necessary to eliminate apparent immediate hazards to the subject as determined by the authority of a physician, to the extent the physician is permitted to do so under applicable federal, state, or local law. FDA regulations at 21 CFR 56.104(c) permit the emergency use of a test article without IRB review when the need for an investigational drug or biologic arises in a situation that does not allow time for submission of an IND. In such a case, FDA may authorize shipment of the test article in advance of the IND submission. Requests for such authorization may be made by telephone or other rapid communication means (<https://www.fda.gov/RegulatoryInformation/Guidances/ucm126491.htm>.) Written documentation of the emergency use must be submitted to the IRB within 5 working days. Any subsequent use of the test article at WMC requires IRB review.